Progression of internal carotid artery stenosis in patients with peripheral arterial occlusive disease

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Objectives: **To study the risk factors and rate of progression of asymptomatic carotid stenosis in patients with peripheral arterial occlusive disease.**

Methods: **Between July 1999 and September 2003, we studied consecutive patients referred to a vascular laboratory for peripheral arterial occlusive disease who had not experienced neurologic symptoms within the previous 3 years. Carotid duplex ultrasound scan (DUS) was performed at baseline and at 6 to 12-month intervals. The internal carotid artery peak systolic velocity (PSV) was used to determine severity of carotid stenosis. Multilevel linear regression modeling (MLM) was used to identify the rate of progression and risk factors for progression.**

Results: **For 614 consecutive patients, median follow-up by DUS was 30 (2-42) months. Patients were 73 ± 10-years-old, and 62% were men. Mean ankle-brachial index (ABI) was 0.79 ± 0.24. The baseline prevalence of carotid stenosis ≥50% (PSV ≥125 cm/second) was 22%. During follow-up, ipsilateral amaurosis fugax, transient ischemic attacks, and strokes occurred in 3 (0.4%), 7 (1.1%), and 5 (0.8%) patients, respectively. Overall, there was little progression in carotid stenosis. Female gender, low ABI, and smoking were risk factors for progression of disease regardless of severity of carotid stenosis. Patients with ≥50% carotid stenosis were at greatest risk of progression if they continued smoking and were diabetic. Prediction models for progression of carotid stenosis given a baseline PSV and patient risk factors were constructed.**

Conclusion: **There are few neurologic events in patients with asymptomatic carotid stenosis. The average rate of progression of stenosis over 2 years is not significant but greater in diabetic patients with baseline stenosis >50% who continue smoking. Rescreening by serial DUS should be limited to high-grade stenosis and follow-up performed at an interval of 1-2 years. (J Vasc Surg 2009;50:292-8.)**

For symptomatic carotid stenosis, randomized controlled trials have documented the benefit of prophylactic carotid endarterectomy (CEA).[1,2] The publication of asymptomatic carotid artery trials[3,4] have demonstrated a small but statistically significant reduction in stroke following carotid endarterectomy for asymptomatic patients. This resulted in an increased interest in identification of asymptomatic patients. The prevalence of moderate-to-severe internal carotid artery stenosis is low in unselected elderly (>70-years-old) healthy volunteers (1.5%).[5] Patients with known peripheral vascular disease, however, have an increased prevalence (32-33%) of hemodynamically significant (>50%) stenosis by duplex ultrasound scan (DUS).[6,7] Because of its sensitivity and specificity,[8,9] and the absence of direct risk, DUS is a useful diagnostic test. Controversy remains regarding the natural history of asymptomatic carotid stenosis, and, therefore, regarding the need for monitoring with repeated DUS and the appropriate interval for reassessment. We followed a large cohort of asymptomatic patients with DUS for assessment of progression of carotid stenosis, and with clinical evaluation for definition of neurologic events, to provide information on the natural history of the disease.

Our group previously identified risk factors for carotid stenosis in this population and examined progression of carotid stenosis over a 6-9-month period.[6] In this work, we present the long-term follow-up (median 30 months) of the same patient cohort with assessment of the risk and rate of progression of stenosis and the occurrence of neurologic symptoms with usual medical management.

METHODS

This is a prospective cohort study of patients, referred by generalists or vascular surgeons, for assessment of lower extremity peripheral arterial occlusive disease to a vascular laboratory accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratory (ICAVL). In addition to the noninvasive hemodynamic testing requested by the referring physician, all patients also underwent carotid duplex ultrasound scans. All results were reported to the referring physician, but no attempt was made to alter management.

Inclusion and exclusion criteria. Consecutive patients referred for noninvasive evaluation of lower-extremity peripheral arterial occlusive disease on the basis of clinical findings were included in the study. Patients were excluded if they had neurologic symptoms or a documented neurologic event within 3 years before entering the study. Arteries were excluded from analysis if they were occluded, an accurate DUS assessment was not available, or if they had

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received either a surgical or endovascular intervention. Patients were excluded from the study if both arteries were occluded.

Data collection. A registered vascular technologist, trained in the assessment of clinical variables by study physicians, administered a standard questionnaire to record demographic data, details of pre-existing risk factors (gender, age, diabetes mellitus, history of smoking, hypertension, prior stroke, and prior coronary artery disease), and clinical outcomes of stroke, transient ischemic attack, amaurosis fugax, and carotid endarterectomy, at each visit. In order to address bias resulting from the collection of clinical outcomes from patients returning for repeat studies (events might be more common in those who did not return), we selected all participants with either artery having greater than 50% stenosis who had not returned for follow-up in the last 12 months of the study for extended clinical follow-up by telephone. Calls were made by one of the physician investigators. Resources did not permit telephone follow-up of all patients who were not seen in the last 12 months of the study.

DUS. A DUS of the carotid arteries was done at the time of entry in the study and repeated at 6 to 12-month intervals by a registered vascular technologist. Color duplex scanning was used to investigate the carotid arteries with a 5 MHz pulsed Doppler carrier, a 1.5 mm cubed sample volume at a 60 degree angle to the axis of the vessel. The internal carotid artery (ICA) and common carotid artery (CCA) peak systolic velocity (PSV) and ICA/CCA ratio were recorded. Carotid stenosis was determined according to Strandness criteria[10] and previously described classification.[9] All results were reported to the referring physicians.

Outcomes and statistical analysis. The primary outcome was progression of carotid stenosis. Studies of this outcome usually use one of the following approaches: (1) Report results for the total number of carotids (right and left); (2) Provide results for right or left carotid arteries separately (considering the artery as the unit of analysis); and (3) Provide results by most severe stenosis (considering the patient as the unit of analysis). It is clear that the first approach is flawed since findings of stenosis in the two carotid arteries of the same patient are not independent observations (an individual has unique properties that affect the progression and presentation of carotid disease); the second and the third approach do not take advantage of the information derived by pooling the total number of carotid arteries available to the researcher. We have addressed this issue using multilevel linear regression modeling (MLM), also known as linear mixed modeling. This is a multivariate analytic technique which takes into consideration the relationships of the two carotid arteries within the same patient and at different time points during the follow-up.[11] MLM explicitly recognizes the clustering of two arteries within each individual and the correlation between them (ie, does not treat them as independent observations). It also allows evaluation of continuous variables with respect to time, and to detect the rate of change within the artery. While life-table analysis is limited to binary assessment of a categorical, MLM does not have any threshold limitation for assessment of the variable under study.

Table 1. Risk factors for atherosclerotic disease

	Mean ± SD; N (%)
Age	72.8 ± 9.5
Male gender	370 (62)
Smoking history	489 (82)
Current smoking	137 (23)
Diabetes	133 (22)
Hypertension	417 (70)
Angina	288 (48)
Myocardial infarction	157 (26)
Remote stroke†	85 (14)
Ankle brachial index	0.79 ± 0.2

SD, Standard deviation; *N,* number.
†More than 3 years before entering the study.

For MLM, the ICA PSV was used to define the severity of carotid stenosis.[9] Since the relationship between the ICA PSV ratio and angiographic-defined carotid stenosis by NASCET is not linear (ie, one unit at the bottom of the scale does not correspond to a percentage stenosis similar to that of one unit at the top of the scale), we used the logarithm of the ICA PSV as a dependent variable for progression of stenosis in the MLM.

All patients with one or more follow-up ultrasound scans were included in the analysis of progression of degree of carotid stenosis. The variables studied were age, gender, smoking history, current smoking, diabetes, hypertension, coronary artery disease, history of stroke, and change in ankle/brachial index (ABI). Data from arteries were censored in the MLM if they reached occlusion, an ipsilateral neurologic event occurred, or if the patient underwent CEA on that side. Clinically important variables or variables that were statistically significant in univariate analysis were entered into a multivariate analysis. Variables were retained in the model if they were significant at the $P < .05$ level.

Regression models were created to predict the severity of carotid stenosis (dependent variable) over 24 months given the degree of baseline stenosis and presence of risk factors. The following formula was used for the prediction model (n = number of months): Log $PSV_{\text{time n months}} = ß_{\text{time}} \times (\text{n months}) + ß_{\text{Risk Factor a}} + ß_{\text{Risk Factor b}} + ß_{\text{time*Risk Factor a}} \times (\text{n months}) + ß_{\text{time*Risk Factor b}} \times (\text{n months})$. Data were analyzed using the statistical software SPSS, version 10 (SPSS Inc, Chicago, Ill). Continuous variables are expressed as mean ± standard deviation.

RESULTS

Population characteristics. From July 1999 to December 2003, 614 patients met eligibility criteria and underwent at least one duplex scan. (Our previous report is of 620 patients;[6] on independent review of eligibility criteria by two authors, 6 patients in the original study did not meet inclusion criteria.) Of this patient population, 547 (89.1%) received at least one follow-up scan and provided data to the analysis of progression of degree of stenosis. The base-

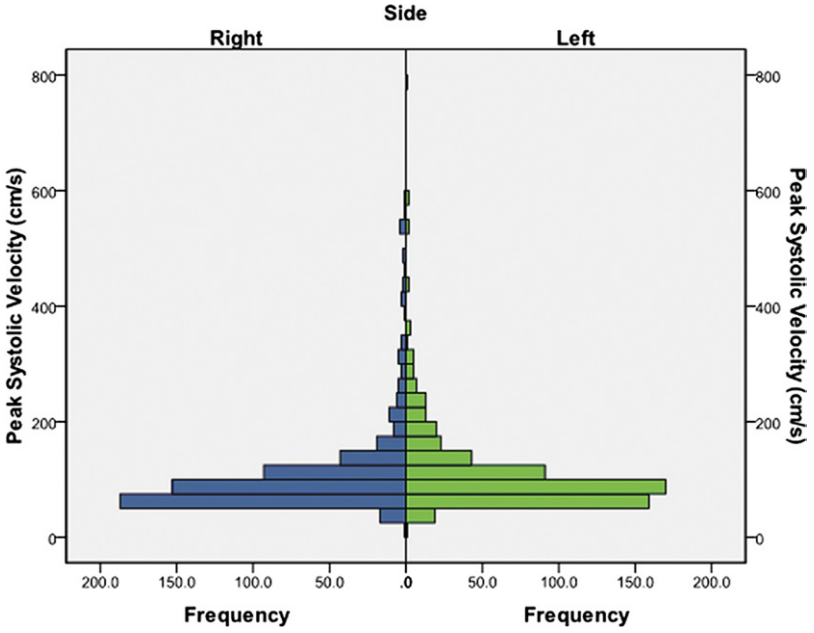

Fig. Distribution of peak systolic velocity in 1159 arteries eligible for study.

line characteristics are described in Table I. Hyperlipidemia and antiplatelet medication status were unavailable for 158 and 132 patients, respectively. For the remainder of patients, 298 (65%) received lipid control medication, 411 (85%) received antiplatelet medication, and 231 (57%) received both.

Degree of carotid stenosis. Severity of carotid stenosis was determined according to previously published criteria.[9] Of the 614 patients, 29 (2%) arteries were occluded, 40 (3%) had prior endarterectomy. There were 1159 arteries eligible for study. Distribution of peak systolic velocity is shown in the Fig.

Ultrasound follow-up. Of the 614 patients originally recruited, 547 received at least one follow-up scan, 490 patients two, 350 patients three, 157 patients four, and 49 patients five. The median period of follow-up by ultrasound scan was 30 (minimum 2, maximum 42) months.

Clinical follow-up. Of the 614 patients, 312 (51%) were last assessed within the last 12 months of the study with DUS and clinical examination. Of the remaining 302 patients, 102 had stenosis >50%: a physician investigator contacted each patient by phone. Of these, 55 were alive and well, 4 had died from stroke (details could not be obtained from the families), 25 died from causes other than strokes, and 18 died from unknown causes. The remaining 200 (33%) patients had no follow-up during the last 12 months of the study because the degree of stenosis did not warrant further follow-up.

During follow-up, 10 (1.6%) patients experienced a non-focal transient neurologic event. Symptoms included speech problems, bilateral visual defects, and dizziness. Focal right hemispheric transient ischemic attacks (TIAs) occurred in 4 patients (0.6%) and 3 patients (0.5%) experienced left hemispheric TIAs, two of which led to CEA. Three patients experienced amaurosis fugaux (0.5%).

From phone interviews, in addition to the four fatal strokes, 6 patients had experienced non-fatal strokes, but could not adequately describe their symptoms to identify the affected side; medical records for these patients were not available. There were three right hemispheric and two left hemispheric strokes recorded from patients assessed in the laboratory. One right hemispheric stroke occurred after an angiography, a second was a complication of CEA. During follow-up, 20 patients underwent CEA, one was prompted by amaurosis fugax, and two were after TIAs. Distribution of neurologic events with respect to baseline stenosis >50% is displayed in Table II. The rate of neurologic events was not statistically different between the two groups.

Progression of carotid stenosis for 0-99% stenosis. As shown in the Fig, most arteries did not have significant carotid stenosis (PSV >125 corresponding to stenosis >50%). In these models, when all carotid arteries within the cohort were studied, history of smoking, currently smoking, female gender, and a decrease in ABI, were associated with progression of carotid stenosis (Table III). In the absence of these risks, average progression did not occur. Examples of average progression of carotid stenosis over 24 months for people with different combinations of these risk factors is given in Table IV. The following formula was used for the prediction model (n = number of months): Log $PSV_{time\ n\ months} = ß_{time} \times (n\ months) + ß_{current\ smoking} + ß_{gender} + ß_{history\ smoking} + ß_{change\ in\ ABI} \times (change\ in\ ABI) + ß_{time*current\ smoking} \times (n\ months) + ß_{time*gender} \times (n\ months) + ß_{time*history\ smoking} \times$

Table II. Distribution of ipsilateral neurologic events according to baseline stenosis for patients in whom the laterality of the event could be determined

Baseline stenosis	*Stroke (%)*	*TIA (%)*	*AMF (%)*	*All neurologic events (%)*
<50%	5/900 (0.5)	3/900 (0.3)	1/900 (0.1)	9/900 (1.0)*
>50%	0/259 (0)	4/200 (2)	2/259 (2.6)	9/259 (2.6)

Ten additional patients were found to have had a stroke (4 fatal, 6 non-fatal) in telephone follow-up, but the association with artery could not be made as the laterality of the stroke could not be determined. The unit of analysis is artery.
TIA, Transient ischemic attack; *AMF,* amaurosis fugaux.
*$P > .05$ for the proportion of events associated with arteries with less than or greater than 50% stenosis.

Table III. Risk factors for progression of carotid stenosis with baseline 0-99% stenosis

Independent variable	*Beta*	*Standard error*	*Antilog beta*	*95% Confidence intervals for antilog beta*		P *value*
Intercept	1.940	1.86×10^{-2}	87.1	80.1	94.7	<.001
Time (in months)	-7.52×10^{-4}	3.10×10^{-4}	0.998	0.997	1.000	.012
Currently smoking (yes)	-1.82×10^{-2}	1.74×10^{2}	0.959	0.887	1.037	.295
Female gender (yes)	3.48×10^{-3}	1.56×10^{-2}	1.008	0.939	1.082	.824
Smoking history (yes)	6.12×10^{-2}	1.91×10^{-2}	1.151	1.056	1.255	.001
Change in ankle/brachial index over two interval observations (each 0.2 decrease)	-1.27×10^{-1}	3.17×10^{-2}	0.746	0.647	0.861	<.001
Time∗Currently Smoking	1.01×10^{-3}	2.63×10^{-4}	1.002	1.001	1.004	<.001
Time∗Female gender	5.96×10^{-4}	2.20×10^{-4}	1.001	1.000	1.002	.007
Time∗Smoking history	7.96×10^{-4}	3.05×10^{-4}	1.002	1.000	1.003	.009
Time∗Change in ankle/brachial index	-1.13×10^{-3}	4.72×10^{-4}	0.997	0.995	1.000	.017

The dependent variable peak systolic velocity (PSV) was log transformed before analysis. Beta coefficients show the mean difference in log PSV, adjusted for other variables in the model, for each unit change (months for time; change in 0.2 for change in ankle-brachial index) or for people with rather than without the other risk factors. Antilog beta shows the model parameter for average difference in PSV for each unit change in a risk factor. The 95% confidence intervals are constructed by taking antilog (beta ± 1.96 standard error) for each variable. The effect size and statistical significance for each variable reflects its association with baseline stenosis. The effect size and statistical significance of the variable ∗time interaction are the measures of their association with progression of carotid stenosis. Because of the log transformation in the model, this is multiplicative (ie, multiply baseline stenosis by 1.002 for each month, in people who were current smokers at baseline).

Table IV. Model predictions for progression of carotid stenosis 0-99% over 2 years

Baseline PSV (cm/second)	*Female gender*	*History of smoking*	*Current smoker*	*Decrease in ABI (each 0.2 decrease)*	*PSV at 2 years cm/second*
75	Y	Y	Y	Y	77
75	Y	Y	Y	N	82
75	Y	Y	N	N	79
75	Y	N	N	N	76
75	N	N	N	N	72
125	Y	Y	Y	Y	128
125	Y	Y	Y	N	136
125	Y	Y	N	N	131
125	Y	N	N	N	126
125	N	N	N	N	119

PSV, Peak systolic velocity; *ABI,* ankle brachial index; *Y,* yes; *N,* no.

(n months) + $ß_{\text{time*change in ABI}} \times$ (n months) × (change in ABI).

Progression of carotid stenosis for 50-99% stenosis. Progression of disease in arteries with significant baseline stenosis (>50%) was associated with currently smoking and diabetes (Table V); as in the previous model, there was no average progression in the absence of these risk factors. Examples of average progression for different combinations of risk factors are given in Table VI. The following formula was used to derive model predictions: Log $PSV_{\text{time n months}} = ß_{\text{time}} \times$ (n months) + $ß_{\text{current smoking}} + ß_{\text{diabetes}} + ß_{\text{time*current smoking}} \times$ (n months) + $ß_{\text{time*diabetes}} \times$ (n months).

There were few patients who suffered a neurologic event. The small size of this group did not permit a meaningful comparison of progression of stenosis between patients who developed a neurologic event and those that remained asymptomatic. During follow-up, carotid steno-

Table V. Risk factors for progression of carotid stenosis from baseline 50-99% stenosis

Independent variable	*Beta*	*Standard error*	*Odds ratio*	*95% Confidence interval for odds ratio*		P *value*
Intercept	2.28	1.86×10^{-2}	192.0	176.6	208.7	<.001
Time (months)	4.28×10^{-6}	3.06×10^{-4}	1.000	0.998	1.001	.989
Currently smoking	3.49×10^{-2}	2.59×10^{-2}	1.084	0.964	1.218	.179
Diabetes	2.41×10^{-2}	2.55×10^{-2}	1.056	0.942	1.186	.346
Time*currently smoking	1.95×10^{-3}	5.68×10^{-4}	1.005	1.002	1.007	.001
Time*diabetes	1.29×10^{-3}	6.15×10^{-4}	1.003	1.000	1.005	.036

Table VI. Model predictions of progression of carotid stenosis from baseline 50-99% over 2 years

Baseline PSV (cm/second)	*Current smoker*	*Diabetes*	*PSV at 2 years (cm/second)*
175	Y	Y	209
175	Y	N	195
175	N	Y	187
175	N	N	175
250	Y	Y	299
250	Y	N	279
250	N	Y	269
250	N	N	250

PSV, Peak systolic velocity.

sis progressed to occlusion in 3 patients. None was associated with a neurologic event.

DISCUSSION

This study prospectively followed progression of carotid stenosis and neurologic events in 614 patients with peripheral vascular disease (PVD). Patients were representative of people with PVD: they were mostly hypertensive men with prior history of smoking, diabetes, and coronary artery disease (Table I). Overall, there was little progression of carotid stenosis. Female gender, history of smoking, currently smoking, and decrease in ABI were risk factors for progression of carotid stenosis when the cohort was assessed as a group. The rate of progression, however, was modest. However, patients with clinically significant baseline stenosis (>50%) who were diabetic and continued to smoke experienced an average progression of degree of stenosis that was clinically important over a 2-year time frame (Table VI). These patients may warrant periodic follow-up as they approach the threshold of benefit from CEA; the optimal frequency of this follow-up remains to be defined.[12,13]

We recognize several important limitations to our study. This is a study of progression in people with a modest prevalence of severe stenosis (6% had >70% carotid stenosis) and should not be generalized to people with high degrees of stenosis at baseline.

We assembled a cohort at high-risk for carotid stenosis based on referral for peripheral vascular studies, but did not document the clinical degree of severity of the peripheral vascular symptoms, and were, therefore, unable to include this in our analysis. Some patients included will undoubtedly have been referred for vascular studies for symptoms not due to PVD.

While ultrasonographic scan follow-up was good, with 89% of patients returning for at least one follow-up examination and contributing to the analysis of progression of stenosis, clinical follow-up, a secondary aim of this study, was less complete. We recognized that the low event rate in people returning for follow-up (5 strokes in 547 patients [1%] over median 30-months of follow-up) might result from biased ascertainment, since people with fatal stroke were missed and people with stroke might be less likely to return for routine follow-up. We selected 102 patients at highest risk, based on a last recorded stenosis of 50% or more, of the 302 people who had not returned for follow-up in the last 12 months. Of these, 4 patients had died from stroke and a further 6 had experienced stroke (10%), bearing out our hypothesis. A sensitivity analysis accounting for a similar stroke rate in the 200 people not evaluated in the last 12 months of the study would give an overall stroke rate for the cohort of 35 strokes in 614 patients (5.7%); if the stroke rate in the 200 people not contacted were more in keeping with those that returned (1%), there would have been 17 strokes in 614 patients (2.8%).

Our approach of censoring at stroke, TIA, or carotid endarterectomy is, of course, statistically biased towards under-estimation of progression. Those very people who have had events, or whose physician has determined that the benefits now exceed the risks of carotid endarterectomy, are those who are most likely to progress. There is no alternative but to censor after carotid endarterectomy, as the anatomy is fundamentally altered by this procedure. We chose to censor after stroke and TIA because each of these is a defining event that alters the patients' status from asymptomatic to symptomatic. Once a patient develops symptomatic disease, the issue of following for progression of asymptomatic stenosis is no longer relevant and a different question of whether the patient will likely benefit or not benefit from endarterectomy on the basis of current severity of stenosis in the affected artery instead needs to be answered. For this reason, we felt that our censoring plan was the most relevant to inform clinical practice in the monitoring of asymptomatic stenosis.

Our models estimate average progression; it is not possible from this approach to estimate proportions progressing in each category as we have in earlier work from

Table VII. Progression of asymptomatic carotid stenosis

Author	*N arteries/patients*	*Baseline stenosis*	*Follow-up (years)*	*Definition of progression*	*Regression*	*Progression*
Rockman[15]	282/246	50-79%	3.2 ± 1.5	Progression to a higher Strandness Category	N/A	1 year-4.9%; 3 years-16.7%; 5 years-26.5%
Liapis[14]	442/332, 66% asymptomatic	31% ≥50%	3.7	Progression to a higher decile of stenosis	N/A	Annual rate 2.8%
Sleight[16]	219/219	50-79% - n = 110 (50%); 80-99% - n = 107 (49%)	4	Progression to a higher Strandness Category or higher decile of stenosis	14%	None
Mansour[17]	458/244	50-79%	2.1 ± 1.1	Progression to a higher Strandness category (>80%)	N/A	15.5% over 2.1 years
Rosamund[18]	N/A/715	<50% n = 357 (50%); 50-79% n = 207 (29%)	3.2 years	Progression to a higher Strandness category (>50%, or >80%). Regression defined as no progression.	9.1%	<50% -19.5% over 2.3 years to > 50%; 50-79-22.2% over 2 years to >80%
Garvey[20]	1470/905	22% >50%	2.5 years	Progression to a higher Strandness category	2.6%	Annual rate 9.3%
Nehler[19]	434/263	<60%	1.7 years	Stenosis >60%	N/A	4% over 18 months

N/A, Not available.

this dataset.[6] However, the low average rates of progression observed provide no support for strategies of repeated screening at intervals shorter than 2 years, particularly in the case of people with baseline stenosis less than 50% or in people without risks. In our models, both for people with 0-99% stenosis and for people with 50-99% stenosis, all of the effect of time on progression is in the interaction terms (time*risk factor); the multiplicative term for the effect of time in the absence of risk factors is very close to unity in both models (Tables III and V), and this is illustrated in our scenarios: people with no risk factors have average PSV at 2 years that is not different from baseline (Tables IV and VI).

The sample size of 1159 arteries represents one of the largest cohorts of asymptomatic carotid stenosis that has been studied. Prior studies of progression of asymptomatic carotid stenosis have reported conflicting results. The rate of progression has ranged from minimal to 9% per year.[14-20] Table VII demonstrates some of the variability amongst the studies. The ICAVL accreditation status of these laboratories is not reported.[14-20] The variability in results can be explained by differences in baseline stenosis of studied populations, medical interventions, technique of DUS assessment, and methods of statistical evaluation of progression. Prior reports have relied upon life-table analysis to determine rate of progression.[14,15,17-20] Progression is defined as a change from a lower category to a higher category of stenosis. Often these categories are based upon the Strandness classification.[10] There are several disadvantages to this approach. In life-table analysis, subjects are censored after they reach an endpoint, in this case progression. Subsequently, possible regression in follow-up examination is not detected. Regression rates as high as 20% in arteries that have shown progression have been reported, some of which may be biological, and some due to variation in measurement.[16]

The reliability of DUS between and within the same laboratories is variable.[9,21-23] Correaveau et al[21] have demonstrated that there is poor interobserver agreement in measurement of PSV. Admittedly, regression analysis relies on PSV since it is a continuous variable. While there may be random error within an individual measurement, it is expected through serial measurements of the same artery, that random error would be reduced.[24] MLM is able to adjust for the variability between serial DUS, since, unlike life-table analysis, patients are not censored at progression and follow-up studies are included.

Life-table analysis is unable to describe the net change in stenosis for the sample population. Life-table analysis of progression will not describe or account for regression of stenosis. This study used MLM which evaluates whether there is an overall progression of stenosis. Our observation of modest progression is similar to observations by Sleight et al[16] who prospectively followed 219 patients assigned to the medical treatment arm of the Asymptomatic Carotid Stenosis Trial (ACST) (Table VII). Patients received clinical examination and duplex scanning at entry, 4 months following randomization, and at 12-month intervals. The median percentage stenosis was plotted against time, and the authors did not notice any net change in stenosis when it was categorized by either Strandness classification or deciles of stenosis. In their report, all instances of progression and regression were followed, and patients regardless of type of change were censored at 4 years. If their analysis was conducted through a life-table method, where patients are censored at the first instance of progression, 51 patients would have achieved progression (resulting in a progression rate of 23% over 4 years). This would have ignored 45 patients who regressed, and also 10 of the 51 patients who progressed, and on repeat DUS were found to have regressed. If the

arteries that progressed (41) and those that regressed (45) are considered together, overall there is no significant progression of disease.

This study is the first to use MLM to assess carotid stenosis. The technique allows arteries from the same patient to be analyzed separately, yet the characteristics that are unique to that patient and artery, are preserved. Through MLM we were able to formulate equations to determine the rate of progression of stenosis for a given baseline stenosis and individual risk factors. We are not aware of any other reports that have produced prediction models of progression.

CONCLUSION

Asymptomatic carotid stenosis did not, on average, progress rapidly in this patient cohort. Patients with baseline stenosis ≥50% who continue to smoke and are diabetic are at increased risk of progression, and may benefit from screening every 2 years. MLM is an effective novel and appropriate statistical method for understanding the natural history of carotid stenosis.

AUTHOR CONTRIBUTIONS

Conception and design: AJ, CSC
Analysis and interpretation: AJ, CMC
Data collection: RB, RM, HS
Writing the article: AJ, CMC, CSC
Critical revision of the article: AJ, CMC, CSC
Final approval of the article: AJ, CMC, CSC, RM, RB
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AJ and CMC contributed equally to this work.

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